

AMENDMENTS TO THE SPECIFICATION:

Please amend the specification as follows:

Please replace the title with the following:

A Method of Identifying a Chemical Entity which is a Hydroxylase Modulator.

Please replace the paragraph beginning at page 3, line 13 with the following amended paragraph:

Description of the Figures

Figure 1: 2OG binding site.

Figure 2: binding of Asn-803.

Figure 3: conformation of CAD at site 1 (SEQ ID NO: 24).

Figure 4: conformation of CAD at site 2 (SEQ ID NO: 25).

Figure 5: figure indicating the turn formed by 802-804 of HIF-CAD at the active site of FIH.

Figure 6: conformation of the turn formed by residues 802-804 of HIF-CAD at the active site of FIH.

Please replace the paragraph beginning at page 18, line 18, with the following amended paragraph:

If desired the valine residue is connected to one or more units of the peptide DESGLPQLTSYDCE- (SEQ ID NO: 1) in the order given e.g. to glutamic acid (E) alone or to, for aspartic acid (D)-cysteine (C)-glutamic acid (E)-, or a longer chain such as PQLTSYDCE- (SEQ ID NO: 2).

Please replace the paragraph beginning at page 35, line 10, with the following amended paragraph:

Catalytic FIH-1 mediated hydroxylation of a synthetic 19 residue peptide corresponding to residues 788-806 of HIF-1 α was confirmed by mass spectrometric analysis of HPLC purified material: Native peptide 19mer $[M+2H]^{2+} = 1026.67\text{Da}$, modified peptide 19mer $[M+2H]^{2+} = 1034.61\text{Da}$, a mass difference of +8Da of the doubly charged ions, corresponding to +16Da in the peptide (oxygen). N-Terminal Edman degradation of the product peptide gave the following sequence: DESGLPQLTSYDCEVxA (SEQ ID NO: 3), where x was not asparagine. The peak from this (16th) cycle of Edman degradation ran to a similar position as the β -hydroxyasparagine standard. Acid hydrolysis of the modified peptide followed by amino acid analysis showed the presence of β -hydroxyaspartic acid only.

Please replace the paragraph beginning at page 41, line 26, with the following amended paragraph:

Table 2. Partial sequence alignment of FIH with a selection of JmjC domain containing proteins (SEQ ID NOS 4-20, respectively, in order of appearance). FIH secondary structure is indicated above the alignment. Selected 2OG binding residues found in FIH are indicated by dark triangles under the alignment and the two iron binding residues by light triangles. SWALL accession numbers are indicated on the left of the alignment.

Please add the following paragraph immediately after the paragraph beginning at page 41, line 26:

Table 3. Coordinates for crystal structures 1, code 1H2K (SEQ ID NOS 21-22), 2, code 1H2L (SEQ ID NOS 21-22), 3, code 1H2M (SEQ ID NOS 21 and 23) and 4, code 1H2N (SEQ ID NO 21).

Please replace Table 2 on page 42 with the table on the next page. A marked up copy of Table 2 indicating the changes is attached at the end of this paper.

	$\alpha 7$	$\beta 8$	$\beta 9$	$\beta 10$	$\beta 11$
Hs Q969Q7	FNWNNINKQQ	---GKRGWQ---	LTSNLLLI	MEGNVTTPA	HYDEQ---QNEFAQIKGY---KRCILFFPPD
Dm Q9VU77	---ELAADLR---	VSDLDEAQQ (4)	---PPDAVNFWL---	DERAVTSMKRPY---	EMVYCVISGH---KDEVLIFPPH
Dm Q9W0M3	---ALKEDIS---	---IPDYCTI (5)	PGAVDIKAWL	PAGTVSEMYDEPK---	HLLLOQVFGS---KRIILAAPA
Hs Q9UPP1	---KIVRKLS---	WVENLWPEEC (4)	PNVQKYCLMSVRDSY	TDFHIDEGGT---	SVWYHVLKGE---KIEYLIIRPT
Ce Q9BI67	---RFVQETIS---	MVNRILNEDV (20)	PKVEQECFLA	MAGSVTDFHVDFFGS---	SVYTHILKGE---KIEYIIRAPT
Ce Q20367	---RFVQDIS---	MAKRLWSDV (11)	PKIEQICAAAMANSY	TDFHVDFFGT---	SVYFHVFKGE (0) KIEYIIRAPT
Dm Q9VHH9	---EIVRQID---	WVDVVRKQ (17)	PKVQKYCLMSVKNCY	TDFHIDEGGT---	SVWYHILRGS (0) KVEFLIIRPT
Sc P40034	---QNDLVDKIV---	SENGHLEKV (11)	PKVTKYILMSVKDAY	TDFHIDFAGT---	SVYNNVISGQ---KRELLIFPPT
Rn Q9R153	---KTDVFEQVM---	WSDGEPF	---RNGQE---	STLWI	SLGAHTPCHLDSYG---CMLVEQVQGR---KRWHLFFPEE
Ce Q9GY14	---FEDDLFHYAD---	DKRPPH	---RWEVM---	PARSGTAIHIDPLG	TSANSLIQGH---KRWVLIIRPI
Dm Q9V6L0	---TILDYVKNQDYN---	IQIDVNT	---AYLYF---	EMKKTTFEAWHTEDMDLY	SINYLHFGAP---KRWYVVRPE
Hs Q94877	---TVLDVVEECCG---	ISIEAVNT	---PYLYF---	EMKKTTFEAWHTEDMDLY	SINYLHFGEP---KRWYAIIRPE
Ce Q9U297	---TILEDNYE---	IKGVNT	---VYLYF---	EMKKTTFEAWHTEDMDLY	SINYLHFGAP---KRWYAIIRPE
Dm Q9V333	---TILNLVNTDYN---	IIIDVNT	---AYLYF---	EMKKTTFEAWHTEDMDLY	SINYLHFGAP---KRWYAIIRPE
Hs Q75164	---TILDVVEKESG---	ITIEGVNT	---PYLYF---	EMKKTTFEAWHTEDMDLY	SINYLHFGEP---KRWYAIIRPE
Dm Q9VJ97	---FASDWLNEQL---	IQCKDDY	---RFVYN---	PKNSWTSYHADVGE	SESWSTNIVGL---KRWLIMPPG
Sp Q13977	---FADDWLNAYV---	IDCESDDF	---RFAYL---	SHLTGLTDPVYASH	SFSVNLGCV---KRWLFIDFK

FIH = Factor Inhibiting HIF
PASS1 = Protein associating with
small stress protein

Hs = Homo sapiens
Dm = Drosophila melanogaster
Ce = Caenorhabditis elegans
Sc = Saccharomyces cerevisiae
Rn = Rattus norvegicus
Sp = Schizosaccharomyces pombe

TABLE 2